METOCLOPRAMIDE
Oral forms, suppositories, injectable forms

COMPANY CORE DATA SHEET

REFERENCED VERSION
FOR INTERNAL USE ONLY

Approval Date: 20 dec 2013  Version: 8.0  Total number of pages:16
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General Information
A Company Core Data Sheet (CCDS) is the company internal basis for development and maintenance of local labeling (i.e., prescribing information, patient information), to ensure consistency of information between countries.

- Mandatory (Bold) text:
  Part of the information in this document is considered Mandatory Information (highlighted in bold print). Mandatory Information is information affiliates are required to submit to their local regulatory authorities for inclusion into their local labeling, without any modification. Exceptions are to be agreed by Regulatory Labeling. [Note: Bolded headings and sub-headings are never considered as mandatory information]

- Non-Mandatory (Non-Bold) text:
  Non-mandatory information does not have to be included in local labeling, however the local text can not contradict the information from the CCDS/CCSI.
  Exceptions are the Indication and Dosage sections: The Company Core Data Sheet also contains information that is not bolded but still is considered mandatory for submission (e.g., indications and dosage recommendations for a newly developed product or any new indication). Again this text is NOT in bold. The affiliates will be informed accordingly when receiving the revised CCDS.
  The indications and dosage/administration recommendations given in the CCDS are restricted to those that are supported by the company, and for which a complete dossier is available. A regional/country specific label may contain all of these, or only a subset. Any significant deviation/modification in the wording of the(se) indication(s) and dosage/administration recommendations, including modifications from discussions with local authorities, should be pre-discussed and agreed upon with Regulatory Labeling prior to implementation.
  As a result of the local/regional agency approval process, the actual approved indications and dosage/administration recommendations in a given country or region may not be identical to those given here.

In this document,
- all Mandatory Safety Information is in bold.
- non-mandatory information is displayed in non-bold.
- references are in Arial Narrow 10.

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The following codes are used:

*TM* represents the local product name of any formulation.
*TM....* represents the local product name of .........
1 DESCRIPTION

1.1 ACTIVE MOIETY(IES) / ACTIVE INGREDIENTS

Metoclopramide

1.2 THERAPEUTIC OR PHARMACOLOGICAL CLASS

ATC code: A03FA Propulsives
Chemical class: benzamide

1.3 PHARMACEUTICAL FORM(S)

Oral forms, suppositories, injectable forms

1.4 COMPOSITION

Active ingredient: Metoclopramide
Metoclopramide combinations: see local dossier
Excipients:
See local dossier

1.5 NATURE AND CONTENTS OF CONTAINER

See local dossier

2 INDICATIONS

Injectable form /IM-IV

Adult population

*TM* is indicated in adults for:
- Prevention of post operative nausea and vomiting (PONV)
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting
- Prevention of radiotherapy induced nausea and vomiting (RINV).

Paediatric population

*TM* is indicated in children (aged 1-18 years) for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option
- Treatment of established post operative nausea and vomiting (PONV) as a second line option

Oral route

Adult population

*TM* is indicated in adults for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV)
- Prevention of radiotherapy induced nausea and vomiting (RINV).
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting. Metoclopramide can be used in combination with oral analgesics as a prokinetic to assist absorption of analgesics in acute migraine.

**Paediatric population**

*TM* is indicated in children (aged 1-18 years) for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option

**Rectal route**

**Adult population**

*TM* is indicated in adults for:
- Prevention of delayed chemotherapy induced nausea and vomiting (CINV)
- Prevention of radiotherapy induced nausea and vomiting (RINV)

3    DOSAGE AND ADMINISTRATION

3.1    GENERAL

**Metoclopramide single agent**

*Applies only to the injectable forms*

The solution can be administered intravenously or intramuscularly.

**All indications (adult patients)**

Prevention of PONV: a single dose of 10 mg is recommended.

Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting and prevention of radiotherapy induced nausea and vomiting (RINV): recommended single dose of 10 mg, repeated up to three times daily.

The maximum recommended daily dose is 30 mg or 0.5 mg/kg body weight.

The injectable treatment duration should be as short as possible and transfer to oral or rectal treatment should be made as soon as possible.

**All indications (paediatric patients aged 1-18 years)**

The recommended dose is 0.10 to 0.15 mg/kg body weight, repeated up to three times daily by intravenous route.

**Dosing table**

<table>
<thead>
<tr>
<th>Age</th>
<th>Body Weight</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>10-14 kg</td>
<td>1 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>3-5 years</td>
<td>15-19 kg</td>
<td>2 mg</td>
<td>Up to 3 times daily</td>
</tr>
</tbody>
</table>
The maximum treatment duration is 48 hours for treatment of established post operative nausea and vomiting (PONV).

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

**Applies only to the oral forms**

**All indications (adult patients)**

The recommended single dose is 10 mg, repeated up to three times daily.

The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.

The maximum recommended treatment duration is 5 days.

Prevention of delayed chemotherapy induced nausea and vomiting (CINV) (paediatric patients aged 1-18 years)

The recommended dose is 0.10 to 0.15 mg/kg body weight, repeated up to three times daily by oral route. The maximum dose in 24 hours is 0.5 mg/kg body weight.

**Dosing table**

<table>
<thead>
<tr>
<th>Age</th>
<th>Body Weight</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
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<tbody>
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<td>1-3 years</td>
<td>10-14 kg</td>
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</tr>
<tr>
<td>3-5 years</td>
<td>15-19 kg</td>
<td>2 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>5-9 years</td>
<td>20-29 kg</td>
<td>2.5 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>9-18 years</td>
<td>30-60 kg</td>
<td>5 mg</td>
<td>Up to 3 times daily</td>
</tr>
<tr>
<td>15-18 years</td>
<td>Over 60 kg</td>
<td>10 mg</td>
<td>Up to 3 times daily</td>
</tr>
</tbody>
</table>

[Appropriate measuring device must be provided with the product, and instructions for use must be included in the SmPC]

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

**For tablets/capsules/granules**

Appropriate additional information regarding posologies adaptation should be implemented in the PI depending on the strength of the formulations

**For formulations which cannot be used to administer a 5mg dose**

Tablets/capsules/granules are not suitable for use in children weighing less than 61 kg. Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

**For formulations which can be used to administer a 5mg dose**

Tablets/capsules/granules are not suitable for use in children weighing less than 30 kg. Other pharmaceutical forms/strengths may be more appropriate for administration to this population.
Applies only to the suppositories

All indications (adult patients)

The recommended single dose is 10 mg, repeated up to three times daily.
The maximum recommended daily dose is 30 mg or 0.5 mg/kg body weight.

The maximum recommended treatment duration is 5 days

3.2 SPECIAL POPULATIONS

Pediatric patients
Use in children less than 1 year of age is contraindicated (see Section 4).23

For metoclopramide combinations
Use in children and adolescents between the ages of 1 and 18 years is not recommended.45

Elderly patients
In elderly patients a dose reduction should be considered, based on renal and hepatic function and overall frailty.6

Hepatic impairment
In patients with severe hepatic impairment, the dose should be reduced by 50%.

Renal impairment
In patients with severe renal impairment (Creatinine clearance ≤ 15 ml/min), the daily dose should be reduced by 75%.
In patients with moderate to severe renal impairment (Creatinine clearance 15-60 ml/min), the dose should be reduced by 50%.7

3.3 ADMINISTRATION

Solution for Injection
Due to the potential risk of severe cardiovascular reactions including cardiac arrest, the solutions for injection are restricted to be used only when appropriate resuscitation equipment is available. (see Section 11)8

4 CONTRAINDICATIONS

For all formulations
- Hypersensitivity to metoclopramide or any of the components.9
- Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.10
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.\textsuperscript{11}

- Confirmed or suspected pheochromocytoma, because of the risk of severe hypertension episodes.\textsuperscript{12}

- Use in children less than 1 year of age due to increased risk of extrapyramidal disorders (see Section 5).\textsuperscript{13}

- Combination with levodopa or dopaminergic agonists because of a mutual antagonism (see section 7)\textsuperscript{14}

- Parkinson’s disease\textsuperscript{15}

- Known history of methemoglobinemia with metoclopramide or of NADH cytochrome-b5 reductase deficiency\textsuperscript{16}

\textit{For rectal formulations}

- Recent history of proctitis or rectal bleeding

- Use in children below 18 years of age.\textsuperscript{17}

5 WARNINGS

- Extrapyramidal disorders may occur, particularly in children and young adults and/or when high doses are used (see Section 11). \textit{These adverse reactions resolve completely after treatment discontinuation. A symptomatic treatment may be necessary} (benzodiazepines in children and/or anticholinergic anti-parkinsonian drugs in adults).\textsuperscript{18}

- Treatment should not exceed 3 months because of the risk of tardive dyskinesia especially in elderly (see section 11)

- Respect the time interval of at least 6 hours specified in the dosage section between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose.\textsuperscript{19}

- Metoclopramide is not recommended in epileptic patients as benzamides may decrease the epileptic threshold.\textsuperscript{20}

- In patients with renal or hepatic impairment, a dose reduction is recommended (see section 3.2)\textsuperscript{21}

- As with neuroleptics, a Neuroleptic Malignant Syndrome (NMS) characterized by hyperthermia, extrapyramidal disorders, autonomic nervous instability and elevated CPK, may occur. Therefore cautions have to be taken if fever, one of the symptoms of a NMS, occurs and metoclopramide has to be stopped if a NMS is suspected.\textsuperscript{22}

- Methemoglobinemia which could be related to NADH cytochrome b5 reductase deficiency has been reported. In such cases, metoclopramide should be immediately and permanently discontinued and appropriate measures initiated Metoclopramide may induce Torsade de Pointes, therefore caution should be exercised in patients with known risk factors for prolongation of the QT interval i.e.: - uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesaemia) - congenital long QT syndrome - bradycardia
Concomitant use of medicinal products that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics (see section 11)).

6 PRECAUTIONS

- IV injections should be made slowly, at least over 3 minutes.

7 INTERACTIONS

Contraindicated combination:
Levodopa: Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism.

Combination to be avoided:
Alcohol: Alcohol potentiates the sedative effect of metoclopramide.

Combinations to be taken into account:
- Anticholinergics and morphine derivatives:
  Anticholinergics and morphine derivatives have both a mutual antagonism with metoclopramide on the digestive tract motility.

- CNS depressants (morphine derivatives, hypnotics, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related): Sedative effects of CNS depressants and metoclopramide are potentiated.

- Neuroleptics:
  Metoclopramide may have an additive effect with neuroleptics on the occurrence of extrapyramidal disorders.

- Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

-Digoxin:
  Metoclopramide decreases digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

-Cyclosporine:
  Metoclopramide increases cyclosporine bioavailability. Careful monitoring of cyclosporine plasma concentration is required.

-Mivacurium and suxamethonium:
  Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

-Strong CYP2D6 inhibitors such as fluoxetine
  Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine.

8 PREGNANCY
Data on pregnant patients (> 1000) indicate neither malformative nor foeto/neonatal toxicity during 1rst trimester of pregnancy. A limited amount of data on pregnant patients (> 300) indicate no neonatal toxicity in other trimesters. Animal studies do not indicate reproductive toxicity. The use of metoclopramide may be considered during pregnancy, if necessary.32

Due to pharmacological properties, as other benzamides, in case of metoclopramide administration before delivery, extrapyramidal disorders in newborn cannot be excluded. 33

9  LACTATION

Metoclopramide is excreted in breast milk and adverse reactions in the breast-fed baby cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from metoclopramide treatment.

10  DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Drowsiness may occur following administration of metoclopramide, potentiated by CNS depressants, alcohol; the ability to drive vehicles or operate machinery can be impaired.34

11  ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:

Very common  $\geq 10\%$; Common  $1$ and $ < 10\%$; Uncommon  $0.1$ and $ < 1\%$;

Rare  $0.01$ and $ < 0.1\%$; Very rare  $0.01\%$. Not known (cannot be estimated from available data).

Nervous system

very common: somnolence 36 37

common: Extrapyramidal disorders, even following administration of a single dose of the drug, particularly in children and young adults (see Section 5)38, parkinsonian syndrome, akathisia

uncommon: acute dystonia and dyskinesia, decreased level of consciousness39

rare: convulsions 40 41

not known: Tardive dyskinesia, during or after prolonged treatment, particularly in elderly patients (see Section 5).42 Neuroleptic malignant syndrome 43

Psychiatric disorders

common: Depression 44

uncommon: Hallucination 45

rare: Confusion 46

not known: Suicidal ideation 47

Gastro-intestinal disorders

common: Diarrhoea 48

Blood and Lymphatic system disorders

not known

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates (see Section 5)49
Sulphaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing drugs.50

**Endocrine disorders**

*uncommon: Amenorrhoea, hyperprolactinaemia

rare: Galactorrhoea

*not known: Gynaecomastia.51

*endocrine disorders during prolonged treatment in relation with hyperprolactinemia (amenorrhoea, galactorrhoea, gynecomastia)

**General disorders and administration site conditions**

*common: Asthenia.52

*uncommon: Hypersensitivity53

*not known: Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation)54

**Cardiac disorders**

*uncommon: Bradycardia, particularly with the intravenous formulation55

*not known: QT prolongation and torsade de pointes (see section 5),56 atrioventricular block particularly with the intravenous formulation, cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see Section 3.3),57 blood pressure increase in patients with or without phaeochromocytoma (see section 4)58

**Vascular disorders**

*common: Hypotension especially with intravenous formulation.59

*uncommon: Shock, syncope after injectable use60,61

12 **OVERDOSE**

12.1 **SIGNS AND SYMPTOMS**

Extrapyramidal disorders and drowsiness, decreased level of consciousness, confusion and hallucination, may occur.

12.2 **MANAGEMENT**

Treatment for extrapyramidal disorders is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian drugs in adults).62

13 **INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST**

14 **ABUSE AND DEPENDENCE**

15 **PHARMACODYNAMICS**
15.1 MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS

Antibacterial spectrum (for an antibiotic)
Breakpoints (for antibiotic)
Susceptible microorganisms (for an antibiotic)
Resistant microorganisms (for an antibiotic)
Resistance (for an antibiotic)

15.2 CLINICAL EFFICACY/CLINICAL STUDIES

16 PHARMACOKINETICS

16.1 ABSORPTION

16.2 DISTRIBUTION

16.3 METABOLISM

16.4 ELIMINATION

16.5 SPECIAL POPULATIONS

Gender
Elderly
Paediatric patients
Hepatic impairment
Renal impairment

17 NON-CLINICAL SAFETY DATA

17.1 ANIMAL PHARMACOLOGY

17.2 ACUTE TOXICITY

17.3 CHRONIC TOXICITY

17.4 CARCINOGENICITY

17.5 MUTAGENICITY

17.6 GENOTOXICITY

17.7 TERATOGENICITY

17.8 IMPAIRMENT OF FERTILITY
18 INCOMPATIBILITIES / COMPATIBILITIES

19 STORAGE CONDITIONS AND SHELF-LIFE

20 PREPARATION AND HANDLING

21 PATIENT INFORMATION

\[1\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[2\] Ref: Article 45 of Paediatric Regulation No. 1901/2006 assessment report
\[3\] Ref: Clinical overview: Safety of metoclopramide injectable formulations versus other formulations, Patricia Fitas, 2 May 2011
\[4\] Ref: Article 47 of Paediatric Regulation No. 1901/2006 assessment report
\[5\] Ref: Clinical overview: Safety of metoclopramide injectable formulations versus other formulations, Patricia Fitas, 2 May 2011
\[6\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[7\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[8\] Ref: Clinical overview: Safety of metoclopramide injectable formulations versus other formulations, Patricia Fitas, 2 May 2011
\[9\] Metoclopramide and allergic reactions, Update report to September 30, 1997
\[12\] Meyler’s Side Effects of Drugs, 14th edition, 1224-1225
\[13\] Clinical overview Metoclopramide safety in neonates and infants less than 1-year old, P. Fitas, 14 March 2011
\[15\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[16\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[17\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[19\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[20\] Referral under Art 31 assessment report: 24 October 2013/EMA/CHMP/579079/2013 Final CHMP referral assessment report following the re-examination procedure Metoclopramide only containing medicinal products
\[21\] Drugs acting on the Central Nervous System, Goodman and Gilman’s, The Pharmaceutical basis of therapeutics, 9th edition, 408
\[23\] Loscher W et al.: Studies on the involvement of dopamine D-1 and D-2 receptors in the anticonvulsivant effect of dopamine agonists in various rodent models of epilepsy, Eur.J.Pharmacol., 1986, 128 (1-2), 55-65


Hellstern A. et al.: Absolute bioavailability of metoclopramide given orally or by enema in patients with normal liver function or with cirrhosis of the liver, Arzneim.Forsch./Drug Res. 1987; 37: 733-736


22 Metoclopramide and Neuroleptic Malignant Syndrome, Synthesis up do August 1997

23 CO Metoclopramide and prolonged QT/torsade de pointes, Patricia Fitas, 06 sep 2013

24 Metoclopramide and Neuroleptic Malignant Syndrome, Synthesis up to August 1997


26 Dipalma J.R: Metoclopramide: A dopamine receptor antagonist, AFP Clinical pharmacology, 1990; vol.41: 919-924

27 Martindale, The complete drug reference, 32nd edition, 1200-1202


30 Metoclopramide CO interaction curares LRC22June07

31 CO Metoclopramide and interactions via CYP2D6 Patricia Fitas, 06jul/2013

32 Postmarketing surveillance synthesis, October 2000 (French) CSI2 updated with Metoclopramide CO pregnancy LRCJune07 (CSI3)

33 Clinical overview Metoclopramide and extrapyramidal disorders in neonates after exposure during pregnancy, Patricia Fitas 03 Jan 2013


35 CO Metoclopramide Frequency category of adverse drug reaction, 15 nov 2012, A. Lachacinski, GPE-CC-2012-00638


37 CO Metoclopramide Frequency category of adverse drug reaction, 15 nov 2012, A. Lachacinski, GPE-CC-2012-00638


39 Metoclopramide CO consciousness disorders LRC 22 june 07

40 Safety synthesis+PSUR 01 May 2000 - 30 Apr 2001

41 CO Metoclopramide Frequency category of adverse drug reaction, 15 nov 2012, A. Lachacinski, GPE-CC-2012-00638

42Wiholm B et al. Tardive dykinesia associated with metoclopramide BMJ Vol 288, 545-547, 1984


44 Postmarketing surveillance synthesis from 1985 to August 1997 updated with metoclopramide CO depression LRCJune07

45 Metoclopramide CO consciousness disorders LRC 22 june 07

46 Metoclopramide CO consciousness disorders LRC 22 june 07

47 CO Metoclopramide and suicidal ideations/suicide attempt, Patricia Fitas, 06 sep 2013


49 Postmarketing surveillance synthesis until August 1997


Metoclopramide and anaphylactic shock particularly after intravenous use. Patricia Fitas, 06 sep 2013.


Metoclopramide and prolonged QT/torsade de pointes, Patricia Fitas, 06 sep 2013.